From Cyclophanes to Molecular Machines

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1.1. Introduction

Molecular machines represent a novel area of chemical research that began, at least in our laboratory, with the preparation [1] of a tetracationic cyclophane (Figure 1) — specifically, the π-electron deficient cyclobis(paraquat-*p*-phenylene) ($CBPQT^{4+}$) $\mathbf{1}^{4+}$. There are two key properties of $\mathbf{1}^{4+}$ that have allowed its chemistry to flourish in our hands and also in those of others [2]. 1) It can interact with guests by π-π stacking and charge-transfer interactions [3] — and, in the case of appropriate guests, by using C–H···O interactions [4] as well. 2) The presence of a rigid cavity helps to trap the guests, giving inclusion complexes. In other words, both energetic and steric effects have made this particular cyclophane very attractive for applications. In this Chapter, we will outline the key achievements, from the emergence of this tetracationic cyclophane in 1988, through its infancy in the 1990s as a facile vehicle for supramolecular exploration, forward to its adolescence, as catenanes and rotaxanes started taking a strong hold of this tetracationic cyclophane, up to the present years of its adult life — earning its keep as the central movable part in numerous molecular machines, harnessed to date in molecular memories, but ready to do real mechanical work in the near future.

(Insert Figure 1 here)

1.1.1. Control over the Location and Motion of Moving Parts in Molecular Machines

A molecular machine [5] is a multicomponent system in which the reversible movement of the components can be controlled by an external stimulus (S). In particular, when a machine is composed of 1) moving parts, and when it is provided with 2) an energy supply, and following 3) a signal to start, can 4) perform work, it is of paramount importance to be able to control the relative locations and motions of the moving parts. It is through the evolving chemistry of the tetracationic cyclophane $\mathbf{1}^{4+}$ that the element of control has been established. First, we describe our development of host-guest complexation and the ensuing preparative chemistry leading to pseudorotaxanes, catenanes and rotaxanes. Then, we discuss how we have introduced control (Figure 2) over the motions of components in – nondegenerate rotaxanes (Type I), and nondegenerate catenanes (Type II), as well as over the dethreading/rethreading of pseudorotaxanes (Type III). Practically, the movement results in a change in properties which produce a signal that allows the operation of the machine to be monitored. The outside stimuli can be photons, electrons, or chemical species, to generate photochemically-, electrochemically- and chemically-driven molecular machines, respectively. The story that will

unfold in this Chapter covers two decades of research developments in the design, customerization and optimization of molecules interlocked with the tetracationic cyclophane. These developments are a testament to the fact that the tetracationic cyclophane has been, and will continue to be an active key component in building nanoscale molecular machines with controllable movements.

(Insert Figure 2 here)

1.2. The Creation of the Tetracationic Cyclophane

Our first synthesis [1] of the tetracationic cyclophane $\mathbf{1}^{4+}$ followed directly from the early research of Hünig [6]. In the Würtzburg laboratories, three cyclophanes that may be considered as constitutionally isomeric forms of $\mathbf{1}^{4+}$, were synthesized. These compounds' acceptor properties were found [6b] to resemble those of the paraquat component. The cyclophanes were modified by us [1] to produce (Scheme 1) yet another isomeric form, namely cyclobis(paraquat-*p*-phenylene). The compound was obtained as its tetrakis(hexafluorophosphate) salt in 12% yield, after refluxing a solution of the bis(hexafluorophosphate) salt $\mathbf{2}\cdot 2PF_6$ and 1,4-bis(bromomethyl)benzene (**3**) in MeCN, followed by counterion exchange using aqueous NH_4PF_6 solution. Whereas $\mathbf{1}\cdot 4PF_6$ is soluble in MeCN and $MeNO_2$, exchanging the counterion to afford the tetrachloride

1·4Cl, confers aqueous solubility upon $\mathbf{1}^{4+}$ but renders it insoluble in MeCN and $MeNO_2$. This counterion-dependent solubility provides the possibility of investigating the receptor properties of $\mathbf{1}^{4+}$ in both aqueous and non-aqueous media, as well as in the solid state. The X-ray crystal structure of **1**·4PF_6 reveals (Figure 3) that $\mathbf{1}^{4+}$ adopts [1] a rigid rectangular box-like conformation of dimensions 10.3 × 6.8 Å in the solid state. Although it was noted [7] that each cyclophane ring is stacked one on top of each other to form continuous open channels, it was the inner dimensions of these channels that was exploited in the host-guest chemistry we investigated in the early days.

(Insert Scheme 1 here)

(Insert Figure 3 here)

1.3. Host-Guest Chemistry with the Tetracationic Cyclophane

1.3.1. Location Control — Host-Guest Chemistry

Host-guest complexation of an aromatic donor included inside the tetracationic cyclophane $\mathbf{1}^{4+}$ is a strict self-assembly process that is thermodynamically driven by the formation of noncovalent bonds, aided by the macrocyclic effect — that is, the location of one molecule inside another can be controlled by noncovalent bonding between each component molecule. A high stability constant K_a for one component relative to the other reflects the integrity of the 1:1 complex.

The host-guest chemistry of the tetracationic cyclophane $\mathbf{1}^{4+}$, which involves complexation between it, the receptor (host), and the substrate (guest), is the traditional starting point to explore its molecular recognition properties. $\mathbf{1}^{4+}$ turns out to be a multipurpose host which can bind effectively with a wide range of substrates [7]. It is interesting to note that, prior to pursuing these complexation studies, the investigation of its molecular recognition led to a useful synthetic outcome — specifically, a new and improved template-directed synthesis of $\mathbf{1}^{4+}$. Moreover, the early work on the host-guest chemistry of $\mathbf{1}^{4+}$ was crucial to the ultimate development of artificial molecular machines.

The first assessment of the molecular recognition properties of $\mathbf{1}^{4+}$ involved [7] three isomeric π-electron rich donors — namely, the dimethoxybenzenes, of which 1,4-dimethoxybenzene (**4**) is the most striking. This π-electron rich aromatic compound and the π-electron deficient tetracationic cyclophane $\mathbf{1}^{4+}$ are representative π-donors and π-acceptors, respectively. As a consequence of the donor-acceptor nature of the 1:1 complex, charge-transfer interactions contribute to the noncovalent bonding that drives the formation (Scheme 1) of the inclusion complex $[\mathbf{1}\supset\mathbf{4}]^{4+}$. 1:1 Stoichiometry was established in MeCN solution for $[\mathbf{1}\supset\mathbf{4}]^{4+}$ with a K_a value of 17 M^{-1}. The presence of a red color in the solution indicated the charge-transfer interaction between the π-electron deficient host and the π-electron rich guest. This charge

transfer interaction was retained in the solid state, as indicated by the red color of single crystals. The crystal structure (Figure 4) of the 1:1 complex [**1**⊃**4**]$^{4+}$ revealed that the neutral hydroquinoid guest is inserted centrosymmetrically through the middle of the tetracationic cyclophane's cavity**.** The principal intermolecular binding interactions in this complex are 1) π-π stacking and charge-transfer interactions [3] between the π-electron rich substrate and the π-electron-deficient bipyridinium units in the receptor and 2) "T-type", edge-to-face C–H···π interactions [8], involving the orthogonally-aligned dimethoxybenzene molecule and the *para*-phenylene units that bridge the paraquat components in the tetracationic cyclophane **1**$^{4+}$.

(Insert Figure 4 here)

The discovery of its inclusion complexation led to an exploration to find out which guests are recognized by the tetracationic host **1**$^{4+}$. It was found that **1**$^{4+}$ is an excellent receptor for a wide range of guests containing π-electron rich aromatic rings, such as dioxynaphthalene-based compounds [9], biphenyl [10], benzidine [10] and indole [11] and their derivatives [12] in both organic and aqueous solutions (Table 1). The tetracationic cyclophane **1**$^{4+}$ was also found to recognize numerous small bioactive molecules by forming stable inclusion charge-transfer complexes. These include amino acids possessing electron-rich aromatic subunits [13], neurotransmitters [14] and phenyl D-

glycopyranosides [15]. Tetrathiafulvalene (TTF), a well-known π-electron donor [16], was found to form a 1:1 inclusion complex with $\mathbf{1}^{4+}$ in both solution and in the solid state [17]. TTF undergoes two consecutive one-electron oxidation processes, a key property that anticipates its use in constructing molecular machines with electrochemically controllable internal movements of components. It is interesting to note that TTF and its derivatives are among the very few non-aromatic compounds that complex strongly with $\mathbf{1}^{4+}$.

(Insert Table 1 here)

The variety of donors that form inclusion complexes with the tetracationic cyclophane $\mathbf{1}^{4+}$ testifies to the importance of a planar electron rich π-system to achieve association. However, the binding strength between the guest and $\mathbf{1}^{4+}$ is not solely determined by the strength of the π-donor. Subtle structural differences, conferred by substituents attached to the donor's core, were also found to play a surprisingly dramatic role in determining the binding strength. A systematic investigation [18] of the effect of long chains, which were attached to the aromatic core of several donor molecules, on the binding affinity of guests with $\mathbf{1}^{4+}$ was conducted. It was found that the presence of oxygen atoms on the donor's side arms was responsible for a majority (Table 2) of the observed binding as a result of C–H···O

interactions [4] between the α-hydrogen atoms of the pyridium rings in $\mathbf{1}^{4+}$ and the oxygen atoms of the polyether chains in the guest. Repetitive insertion of ethylene glycol units into the side chains indicates that the binding affinity of the guest toward the tetracationic cyclophane increases with elongation by one ethylene glycol unit, before reaching a plateau after the attachment of two ethylene glycol units: elongation of the side chains with further ethylene glycol units has little effect on the strength of the complexation. This side-chain effect suggests that the C–H···O interactions were satisfied, both sterically and electronically, in the case when the side chains are diethylene glycol units because they are sufficient to support the strongest possible binding. There is a further important point. Neither the aromatic core nor the side arms of the guest bind well by themselves, but together they exert a substantial *cooperative* effect which directs the formation of a stable inclusion charge transfer complex.

(Insert Table 2 here)

In a separate study [19], the influence of the donor's electronic properties on the strength of complexation between a number of different TTF derivatives and the tetracationic cyclophane $\mathbf{1}^{4+}$ has been investigated. The results demonstrate that the strength of association between the donors (TTF derivatives) and the acceptor ($\mathbf{1}^{4+}$) is strongly

dependent on the strength of the donor, which is determined by 1) the first redox potential, and 2) the size of the donor's π surface.

The formation of strong inclusion complexes between $\mathbf{1}^{4+}$ and π-electron rich substrates was recognized [20] as the signal to use appropriate donors as templates to direct the formation of the host molecule. Template-directed synthesis [21] has proved to be a very efficient strategy in optimizing the yield of $\mathbf{1}^{4+}$. In the presence of a template, such as the hydroquinone-based diol **5** (Scheme 2), the yield of the cyclophane was raised from 12% to 45% when the reaction was carried out in DMF. The yield was further improved to 62% when the reaction was performed under ultra-high pressure (10 kbar). Under the same reaction conditions, but using a different template — that is, the 1,5-dioxynaphthalene-based polyether **6**, the efficiency of the template-directed synthesis was raised up to a remarkable yield of 81%.

(Insert Scheme 2 here)

The extensive investigation of the molecular recognition properties of $\mathbf{1}^{4+}$, not only contributed to advances in its synthesis using template-directed protocols, but also provided the background for its inclusion in a range of mechanically interlocked molecules.

1.4. Catenane Chemistry with the Tetracationic Cyclophane

The ability of the tetracationic cyclophane $\mathbf{1}^{4+}$ to form inclusion complexes provides us with the unique opportunity to construct large, ordered molecular assemblies such as catenanes and rotaxanes, using the templating actions inherent in the interlocked compounds themselves as they are formed.

The first catenane incorporating the tetracationic cyclophane was synthesized [22] in the remarkably high yield of 70%, simply by stirring a mixture of the bis(hexafluorophosphate) salt **2**·$2PF_6$, bisparaphenylene[34]crown-10 (**7**) and 1,4-bis(bromomethyl)benzene (**3**) in MeCN for two days. A proposed mechanism for the formation of the [2]catenane is shown in Scheme 3. Alkylation of **2**·$2PF_6$ with the dibromide **3** affords a tricationic intermediate which is bound by the macrocyclic polyether **7** with a pseudorotaxane-like geometry. The subsequent macrocyclization to give the tetracationic cyclophane component is template-directed by the π-electron rich component **7** of the pseudorotaxane-like intermediate to afford the [2]catenane **8**·$4PF_6$ after counterion exchange. The X-ray crystal structure (Figure 5) of **8**·$4PF_6$ shows quite beautifully the mutually interlocked nature of the two component rings. A π-donor/π-acceptor/π-donor/π-acceptor stack (Figure 5b) is formed all the way along one of the crystallographic

directions by the complementary aromatic units, which are separated by the interplanar π-π distances of about 3.5 Å.

(Insert Scheme 3 here)

(Insert Figure 5 here)

In solution, the tetracationic cyclophane and macrocyclic polyether ring components of the [2]catenane $\mathbf{8}^{4+}$ are free to circumrotate through each others' cavities. Exchange of the "alongside" and "inside" hydroquinone rings (Process I in Scheme 4) is achieved by circumrotation of the macrocyclic polyether component through the cavity of the tetracationic cyclophane. Exchange of the "alongside" and "inside" bipyridinium units (Process II in Scheme 4) is achieved by circumrotation of the tetracationic cyclophane through the cavity of the macrocyclic polyether component. The free energies of activation associated with Processes I and II have been obtained by variable temperature ^{1}H NMR spectroscopic investigations. While these investigations reveal a certain degree of freedom for the circumrotation processes at higher temperatures, their motions are found to be frozen out at lower temperatures. Provided it is possible to control the circumrotational motions of the rings, then it should be possible to adapt degenerate catenanes to operate like machines at the molecular level.

(Insert Scheme 4 here)

Macrocyclic polyethers incorporating a variety of π-electron-rich aromatic units, such as 1,5-dioxynaphthalene (DNP) [23] and resorcinol [24] ring systems have also been shown to act successfully as templates for the formation of the tetracationic cyclophane, thus generating [2]catenanes. In addition, introduction of two different π-electron-rich aromatic residues within the same macrocyclic polyether component of a [2]catenane leads to a wide range of molecular structures [25]. In fact, there is a large family of [2]catenanes based on the tetracationic cyclophane $\mathbf{1}^{4+}$ which incorporate different π-donors in the macrocyclic polyether's constitution. Not only can two different π-donors be incorporated, but the positions of their substitution by the polyether linkages can also be varied and even further modifications can be brought about by changing the lengths of each polyether chain [26]. The myriad of [2]catenanes reflects one common theme characterizing the synthesis of interlocked molecular compounds — it is modular.

In those [2]catenanes where there are two donors with differing affinities for binding inside the cavity of the tetractionic cyclophane, two translational isomers are observed. Depending on the relative affinities of each donor for the cyclophane, two different kinds of translational isomerization can be observed. When one of the donors displays a markedly higher affinity for the tetracationic cyclophane, it is localized in the cavity almost exclusively and an "all-or-nothing" situation ensues. For example, a [2]catenane with TTF and DNP units in the macrocyclic

polyether [27] exists as only one translational isomer with the TTF inside the cavity of the cyclophane as determined in solution by ^{1}H NMR spectroscopic studies and in the solid state by X-ray crystallography. In the second case, where the two donors compete for binding inside the cyclophane, an unequal population of the two translational isomers is observed. For example, when DNP and 1,4-hydroquinone (HQ) are in the macrocyclic polyether [25a], there is a 65:35 distribution in CD_3COCD_3 solution where the translational isomer with the HQ ring located inside the cavity of the cyclophane predominates over the translational isomer of the DNP unit inside. The characterization of the translational isomer distribution provides insight for the design and construction of molecular switches wherein control over the location of the two rings needs to be enforced.

1.4.1. Going for Gold — The Story of Olympiadane

The remarkably efficient template-directed syntheses of the [2]catenanes provided the foundation to extend this approach to the self-assembly of [n]catenanes incorporating more than two interlocking ring components. Increasing the size of either the π-electron rich or the π-electron deficient macrocyclic components of the [2]catenane $\mathbf{8}^{4+}$ made it possible to construct [28] a large number of different higher catenanes, such as a [5]catenane (known as Olympiadane) and a branched [7]catenane [29].

(Insert Scheme 5 here)

Two enlarged macrocycles based on π-electron rich and π-electron deficient components, respectively, were designed for use in the self-assembly of a [3]catenane. An additional 1,5-dioxynaphthalene unit was incorporated into the macrocyclic polyether **9**, which was used as the template for directing the synthesis of the enlarged tetracationic cyclophane, cyclobis(paraquat-4,4′-biphenylene) [29]. Reaction (Scheme 5) of the bis(hexafluorophosphate) salt **10**·$2PF_6$ — in which the two bipyridinium units are now separated by longer bitolyl spacer unit — with the dibromide **11** in the presence of **9** at room temperature and ambient pressure gave a [3]catenane $\mathbf{13}^{4+}$ in a yield of 10%, together with a small amount (3%) of the [2]catenane $\mathbf{12}^{4+}$. In the [3]catenane $\mathbf{13}^{4+}$, two of the three π-electron rich aromatic units of each macrocyclic polyether are not occupied by a tetracationic cyclophane. As a result, additional tetracationic cyclophanes can subsequently have their synthesis directed by the 'free' aromatic templates remaining on each of the two π-electron rich macrocyclic polyether components, giving rise to higher [n]catenanes [30] (n = 4 – 7). Further reaction of the [3]catenane $\mathbf{13}^{4+}$, with the bis(hexafuorophosphate) salt **2**·$2PF_6$ and the dibromide **3** at ambient temperature and pressure, gave the [4]catenane $\mathbf{14}^{8+}$ and Olympiadane — the [5]catenane $\mathbf{15}^{12+}$ — in yields of 31% and 5%, respectively. Remarkably, on using ultra-high pressure

(Scheme 6), a [7]catenane **18**$^{20+}$ was also isolated in 26% yield, together with Olympiadane **15**$^{12+}$ (30%), another [5]catenane **16**$^{12+}$ in only trace amounts — which is isomeric with Olympiadane — and a [6] catenane **17**$^{16+}$ (28%). No [4]catenane **14**$^{8+}$ was isolated from the reaction mixture. The X-ray structural analysis of Olympiadane **15**$^{12+}$ reveals (Figure 6a) the nature of five macrocycles that are interlocked linearly with each other, thus facilitating maximized potential for π-π stacking between the components. The π-π stacking interactions within the Olympiadane are augmented by a series of C–H···π and C–H···O interactions (not shown in Figure 6a). Despite the absence of any intermolecular π-π stacking interactions involving the smaller tetracationic cyclophanes, the [5]catenane molecules aggregate to form sheets that are essentially coplanar with the mean planes of these smaller cyclophanes. Furthermore, the X-ray structural analysis of the [7]catenane **18**$^{20+}$ reveals (Figure 6b) a molecular structure that offers every one of the anticipated recognition sites that were designed into the interlocked molecule for π-π stacking — that is, all of the six π-electron rich 1,5-dioxynaphthalene units are utilized in a mutually compatible manner.

(Insert Scheme 6 here)

(Insert Figure 6 here)

1.5. Rotaxane Chemistry with the Tetracationic Cyclophane

Rotaxanes can be prepared using the same strategies as those employed for the self-assembly of catenanes — that is, the mutual recognition of π-electron deficient and π-electron rich aromatic units, can be utilized for the interlocking of the tetracationic cyclophane around a linear dumbbell-shaped component under template control.

Simple [2]rotaxanes, incorporating π-electron-rich aromatic cores, can be self-assembled using two different procedures (Scheme 7). Clipping is the specific name given to the formation of a tetracationic cyclophane around the dumbbell component by utilizing the same template-directed protocol as that used successfully in the [2]catenane synthesis. An alternative approach relies on threading an unstoppered dumbbell through the cavity of the tetracationic cyclophane to form, in the first instance, a pseudorotaxane. A rotaxane is formed subsequently by covalently bonding bulky stoppers onto the ends of the rod. In both cases, the template effect of the π-electron-rich guest dictates the outcome of the reactions to give the desired [2]rotaxanes.

(Insert Scheme 7 here)

Our investigations on the host-guest chemistry of the tetracationic cyclophane $\mathbf{1}^{4+}$ had already established a range of different π-electron rich guests. From the list of guests, it was possible to synthesize [2]rotaxanes incorporating different aromatic units, such as HQ [18, 31],

DNP [18], benzidine and 4,4′-biphenol [10]. While both approaches to rotaxane formation have been employed, clipping has become the preferred method of choice because of its relative simplicity.

A two-station [2]rotaxane can be prepared by adding a second π-electron-rich donor into the dumbbell component. The presence of a second station enables "shuttling" of the tetracationic cyclophane to occur along the rod section of the dumbbell. The first molecular shuttle **19**$^{4+}$, which relies upon this design, was prepared [32] in 32% yield by clipping (Scheme 8) the two components of the cyclophane around the two-station dumbbell **20**. At room temperature in CD_3COCD_3, the tetracationic cyclophane moves back and forth like a shuttle (Scheme 9) between the two identical HQ rings on the rod 500 times per second, a speed which corresponds to an energy barrier of 13.0 kcal mol^{-1}. This shuttle has served as the prototype for the construction of intricate molecular machines.

(Insert Scheme 8 here)
(Insert Scheme 9 here)

1.5.1. Location Control — Catenanes and Rotaxanes

Mechanically interlocked molecules demonstrate the high degree of control over the mutual location of the tetracationic cyclophane with respect to different donors that was first observed in the host-guest chemistry of **1**$^{4+}$. The higher level of complexity represented by the two interlocked rings in catenanes and the interlocked ring and dumbbell

components in rotaxanes allows for the circumrotations and shuttling, respectively. These movements give rise to different translational isomers that are in dynamic equilibrium. Introducing two donors with differing affinities for the cyclophane offers the opportunity to isolate only one of the two possible translational isomers. Furthermore, by considering the options to turn off the noncovalent bonding, the cyclophane can be induced to move to the other donor, thus providing the opportunity to control its movements.

1.6. Switchable Rotaxanes, Catenanes and Pseudorotaxanes

The evolving chemistry of $\mathbf{1}^{4+}$ has provided examples of location control and a demonstration of dynamically moving molecular parts. In order to realize a molecular machine, control over the *movements* of the tetracationic cyclophane had to be addressed through the development of switchable rotaxanes, catenanes and pseudorotaxanes. In particular, the movements have to be attained by switching off and on the recognition elements binding the donor and acceptor together, using chemical, electrochemical and photochemical means to do so.

1.6.1. Controllable Molecular Shuttles

Removing the symmetry in the two-station molecular shuttle by inserting nonidentical “stations” within the polyether thread portion of the dumbbell component provides the opportunity to address the two

stations selectively. The stronger station's binding with the tetracationic cyclophane can be removed by chemical or electrochemical means, allowing the cyclophane to move to the other weaker station. The first switchable molecular shuttle $\mathbf{21}^{4+}$ we reported [33] incorporated (Scheme 10) benzidine and a 4,4′-biphenol units as the two π-electron rich donors. The rotaxane $\mathbf{21}^{4+}$ exists as two translational isomers in a ratio of 84:16 in CD_3CN solution at –44 ˚C, with the tetracationic cyclophane located preferentially on the more π-electron rich benzidine ring system. When an excess of deuterated trifluoroacetic acid is added to the solution, only one $[\mathbf{21 \cdot 2D}]^{6+}$ of a number of possible translational isomers, in which the 4,4′-biphenol residue is encircled by the cyclophane, is observed. This dramatic change in structure is brought about by protonation of the basic nitrogen atoms associated with the benzidine ring system. Addition of deuterated pyridine returns the solution to neutrality, and reinstates the previous distribution of translational isomers in $\mathbf{21}^{4+}$. Furthermore, this switchable molecular shuttle can also undergo reversible electrochemical switching. Monoelectronic oxidation of the more π-electron-rich benzidine residue switches the structure to one in which the radical form $\mathbf{21}^{\cdot 5+}$ experiences the encirclement of the 4,4′-biphenol unit selectively by the tetracationic cyclophane. Both the chemical and electrochemical switching processes are completely reversible. This [2]rotaxane demonstrates the reversible switching off and on of one of the molecular

recognition units, concomitant with the movement of the cyclophane ring from one station to the other.

(Insert Scheme 10 here)

An amphiphilic molecular shuttle **22**·4PF_6 incorporating a monopyrrolo-TTF unit and a DNP ring unit within its rod section was designed in order to utilize the reversible oxidation of the monopyrrolo-TTF unit to turn off its binding with the tetracationic cyclophane. The rotaxane was synthesized [34] using a clipping strategy (Scheme 11). The dumbbell-shaped compound **23** was used as the template for the formation of the encircling tetracationic cyclophane from its precursor **2**·2PF_6 and 1,4-bis(bromothyl)benzene (**3**). The [2]rotaxane **22**·4PF_6 was isolated as an analytically pure brown solid after column chromatography. ^{1}H NMR and UV-visible absorption spectroscopic investigations indicated the coexistence of the two translational isomers — one with the cyclophane encircling the monopyrrolo-TTF unit (**22**·4PF_6-Green), and the other with the cyclophane encircling the DNP ring system (**22**·4PF_6-Red). The translational isomer **22**·4PF_6-Red can be isolated by preparative thin layer chromatography and has been shown subsequently to isomerize slowly in solution to **22**·4PF_6-Green, until such times as an approximately 1:1 mixture exists at equilibrium. The first order kinetics associated with this shuttling process has been measured

and corresponds to an activation free energy barrier ($\Delta G^{\ddagger}$) of 24 kcal mol^{-1}.

(Insert Scheme 11 here)

The shuttling process of **22**·$4PF_6$ provides a working efficiency of no more than 50% to a molecular switch. In order to achieve higher efficiencies, we needed to build a two-station shuttle 1) that favors thermodynamically one translational isomer so that the cyclophane resides preferentially on one site, 2) in which the shuttling process between the two inequivalent states is extremely slow, reflecting a reasonably high activation free energy barrier between the two states, and 3) where there exists a clear means to switch between the two states when an appropriate stimulus is applied. The three requirements for an efficient molecular machine have been fulfilled by using TTF and DNP as the two donor units in a [2]catenane as well as in a [2]rotaxane.

1.6.2. Switchable Catenanes

A [2]catenane **24**·$4PF_6$ comprising (Scheme 12) a tetracationic cyclophane and a macrocyclic polyether ring with two π-electron-rich recognition sites — namely, a DNP ring system and a TTF unit — has been constructed [27]. The X-ray crystal structure of **24**·$4PF_6$ reveals that the TTF unit resides preferentially inside the cavity of the tetracationic cyclophane, an observation which is consistent with the

solution-state behavior indicated by the ^{1}H NMR and UV-visible spectra. The circumrotation (Scheme 12) of the macrocyclic polyether component through the cavity of the tetracationic cyclophane can be induced reversibly by oxidizing and then reducing the TTF unit. When the TTF unit is oxidized, a charge-charge repulsive force between its single (or double) positive charge and the four positive charges on the cyclophane drives the circumrotation of the macrocyclic polyether to position the DNP ring system inside the cavity of the tetracationic cyclophane. Upon reduction of the oxidized TTF unit back to the neutral state, the macrocyclic polyether once again circumrotates through the cavity of the tetracationic cyclophane, returning the [2]catenane to its original state. The switching process can be controlled by both chemical and electrochemical means.

(Insert Scheme 12 here)

1.6.3. Switchable Rotaxanes

Aside from the circumrotary motion of the cyclophane observed in catenanes, the shuttling motion of the cyclophane in rotaxanes can also be controlled by the judicious design of the recognition sites located within the polyether rod component. A [2]rotaxane **25**·4PF_6 was designed [35] and synthesized (Scheme 13) with a tetracationic cyclophane encircling its dumbbell component incorporating TTF and DNP recognition sites, such that the cyclophane is located exclusively

around the TTF unit in the ground state. The redox-switching process in solution was probed by UV-visible and ^{1}H NMR spectroscopies. When the TTF unit is oxidized, the cyclophane moves a remarkable 3.7 nm along the rigid *p*-terphenyl spacer from the TTF to the DNP recognition site. The reduction of the $TTF^{+\bullet}$/TTF^{2+} back to its neutral state, switches the TTF unit back on as a strong donor-based recognition site, thus allowing the concomitant movement of the cyclophane back to its starting position — the ground state of the [2]rotaxane.

(Insert Scheme 13 here)

1.6.4. Photochemically Switchable Pseudorotaxanes

In addition to the controllable movements of the tetracationic cyclophane in rotaxanes and catenanes, the dethreading/rethreading of π-electron rich guests through the cavity of $\mathbf{1}^{4+}$ in a pseudorotaxane also constitutes mechanical motion.

The dethreading/rethreading mechanism of the [2]pseudorotaxane $[\mathbf{1}\supset\mathbf{26}]^{4+}$ can be photochemically stimulated [36,37] and so can be likened to a photo-driven molecular switch. The [2]pseudorotaxane $[\mathbf{1}\supset\mathbf{26}]^{4+}$ is formed (Scheme 14) by adding the thread-like 1,5-dioxynaphthalene derivative **26** to an aqueous solution of the chloride salt of the tetracationic cyclophane $\mathbf{1}^{4+}$. In the presence of a “sacrificial” reductant (**Red**, triethanolamine), the photosensitizer (**P**, 9-anthracenecarboxylic acid) can be excited (Process 1) by light and

transfer an electron to one of the bipyridium units in the cyclophane (Process 2 in Scheme 14). The oxidized species $\mathbf{P}^{+}$ can be rapidly scavenged by the sacrificial reductant to prevent the back electron-transfer reaction and hence the pseudorotaxane remains reduced. As a consequence, the charge-transfer interaction between the thread and the ring is permanently lowered and the dethreading process takes place spontaneously. When oxygen is allowed to enter the irradiated solution, the reduced cyclophane is promptly re-oxidized and **26** again threads through its cavity. This controllable pesudorotaxane represents a prototype at the supramolecular level for a simple molecular machine in which the changes in the relative positions of the components can be followed readily by monitoring differences in absorption and luminescence spectra.

(Insert Scheme 14 here)

1.6.5. Control of Motion

It has been by investigating non-degenerate two-station rotaxanes and catenanes that we have learnt how to control the movements of the tetracationic cyclophane with respect to encircled dumbbells and threaded rings. Control over the cyclophane's location is established by giving markedly different affinities to the two donors and by increasing the kinetic barrier to shuttling. This "all-or-nothing" situation can then be capitalized upon by turning off one of the recognition sites, thus

allowing the cyclophane to relocate around the unchanged donor unit. By utilizing an electrochemically active donor, this movement can be electrochemically powered in a repeating manner by turning on or off an electrical switch. These characteristics constitute all of the requirements for an artificial molecular machine to be put to work in a functioning system. The first demonstration was in the fabrication of molecular memory.

1.7. Electronic Devices Containing Molecular Switches

Catenanes and rotaxanes incorporating the tetracationic cyclophane have been used [38] to fabricate molecular switches that form the key active component in electronic devices. With the ability to control the locations and the relative movements of the cyclophane now well established, the molecular switches have been incorporated [39] into devices with crossbar architectures. A variety of switchable catenanes and rotaxanes have been deployed [38,39] in a range of devices in order to investigate 1) the influence of molecular structure on device function and 2) to explore the opportunities for miniaturizing the overall device. The idea of introducing molecules into electronic devices is not new [40]. It is a logic step that follows from the miniaturization of electronic components predicted by Moore's Law. Researchers, in academia and industry alike, are now considering alternatives, such as the development of nanoelectronic devices based on molecular-scale

switches [41-43] and nanowire-based systems [44]. While these latter systems might be more readily integrable with current microelectronics and represent a natural evolution in CMOS technology, they lack the flexibility and performance, which is represented by the internal structure, inherent in a switchable molecule. The simplest device that can be imagined consists of a single crossbar of two electrodes, between which are sandwiched molecular switches [44].

1.7.1. A [2]Catenane-Based Electronic Device

The first fabrication of a crossbar device [38], utilizing a redox-switchable interlocked molecule, was based (Figure 7) on the switchable [2]catenane **24**$^{4+}$. The general method for constructing such devices relies upon depositing a Langmuir-Blodgett (LB) monolayer of *closely-packed* molecular switches onto a polysilicon electrode. A top electrode of Ti, followed by Al, is subsequently vapor-deposited on top of the monolayer. Amphiphilicity is required to direct the formation of the LB monolayers. In [2]catenanes, hydrophilicity is conferred from the tetracationic cyclophane with its high ionic character, and hydrophobicity is obtained (Figure 7a) by employing a co-surfactant in the form of dimyristoylphosphatidyl anion (DMPA$^-$) as the counterion [45]. High quality, closely-packed films produced from switchable [2]catenanes are essential for preventing the Ti, which is deposited on top, from penetrating through the monolayer and causing a short circuit.

In this example, the fabrication of a working device relies on customizing the molecular switches based on the recommendation from device manufacturers. Such a cross-disciplinary interaction also operated in reverse and thus the devices were modified in order to accommodate the peculiarities of the molecules.

(Insert Figure 7 here)

The molecular devices display switching between high and low conductance states. Each device is interrogated and characterized by applying a 'write' voltage, *V* and recording the 'read' current, *I*. Of the two *I*-*V* measurements, the remnant molecular signature is used to characterize 1) the threshold voltages that are required for switching and 2) the magnitudes of the high and low current values. The binary switching behavior allows for the device's performance in an electronics context to be measured. The remnant molecular signature (Figure 7b) tracks the read current (y axis) as the writing voltage (x axis) is cycled around a loop in 40 mV steps, from 0.0 V to +2.0 V, down to –2.0 V, and back to 0.0 V. In order to record the read current a read voltage of +100 mV is applied in between each of the 40 mV pulses. For the [2]catenane-based crossbar, a low current is recorded, corresponding to the OFF state of the device, until the threshold voltage of +2 V is reached, whereupon a higher current is read, effectively switching the device into an ON state. The ON state is maintained until the threshold

voltage for switching the device back into a low current or OFF state at –1 V is reached. The binary behavior is recorded (Figure 7c) in a separate experiment by reading the current after the device is alternately cycled between ON and OFF states by writing at the threshold voltages. These data reveal that, in addition to the reversible voltage-gated switching of the device ON and OFF more than 10 times, the ON state is metastable, displaying a temperature-dependent resetting of the device back to the OFF state.

A molecule-based nanoelectromechanical switching mechanism, which is consistent with all of the data, has been proposed (Figure 7d) to account for the device's observed experimental behavior. The OFF state corresponds to the co-conformer with the TTF unit inside the cyclophane. In the device, application of a +2 V bias to the Si electrode generates an oxidized form ($TTF^{+\bullet}$ or TTF^{2+}) of the TTF unit in the [2]catenane. Just as in solution, the resulting charge-charge repulsive force drives a circumrotational process, thus positioning the DNP ring system inside the tetracationic cyclophane. When the bias is lowered to +100 mV for the purposes of reading the device, the charge on the molecule is neutralized and yet the DNP ring system remains trapped inside the cavity of the cyclophane on account of the mutually attractive noncovalent interactions. This new co-conformer is responsible for the high-conductance ON state. The device is observed to decay to the OFF state in a manner that is qualitatively similar to the movements of the

tetracationic cyclophane in bistable [2]rotaxanes, self-assembled [46] onto a gold electrode. Therefore, the decay rate is concomitant with the thermally activated circumrotation of the TTF unit back into the central cavity of the cyclophane. Alternatively, applying a reverse bias of –2 V can allow a circumrotation to take place that also leads back to the thermodynamically favored co-conformer. The net reducing voltage causes the reduction of the tetracationic cyclophane, removing its ability to form strong noncovalent bonds with the crown ether component, thus allowing the facile formation, by circumrotation, of the most stable co-conformer.

1.7.2. Bistable [2]Rotaxane Electronic Devices

Crossbar devices built around (Figure 8) the amphiphilic bistable rotaxane **27**$^{4+}$ have been investigated [39] for their ability to switch. The switching displayed by this [2]rotaxane in solution is almost identical to that displayed by the switchable [2]catenane **24**$^{4+}$. Similarly, the devices display an almost one-to-one correlation in terms of remnant molecular signatures and the binary switching behavior of the devices. Note, however, that the catenane switch has an ON/OFF ratio of 2 – 3: in the rotaxane, it goes up to 10. By contrast, control devices based on dumbbell components and non-redox active molecules did not display any switching behavior. These data are consistent with the existence (Figure 9) of a similar nanoelectromechanical mechanism

involving voltage-gated control over the tetracationic cyclophane's location operating in the amphiphilic bistable [2]rotaxanes within the devices, just as was proposed for the switchable [2]catenane **24**$^{4+}$. The only significant difference is that the cyclophane undergoes a linear mechanical movement rather than a circumrotational one. The physical basis behind the changes in the measured conductance between the ON and OFF states is attributed to the switching of the TTF unit's molecular energy levels into and out of resonance with electron tunneling pathways at the energies that are preset by the reading voltages. This hypothesis has been evaluated by first-principles computation. In these studies, the current was calculated as a function of voltage by simulating a crossbar device with a model system based on a single molecule held between electrodes that were represented by clusters of three gold atoms. The computational results confirm [47] that the ON and OFF states correspond to the co-conformers with the DNP ring system and TTF unit encircled by cyclophane, respectively.

(Insert Figure 8 here)

(Insert Figure 9 here)

1.7.3. Memory Devices

A simple crossbar provides the basic element from which to construct [38] a molecular random access memory (RAM) chip. An 8×8 crosspoint structure, comprised in total of 64 crossbars containing a

monolayer of two-station [2]rotaxanes, was constructed [39] to demonstrate a 64-bit memory. In order to write to just one crosspoint, one of the leads is set to +1 V and the other –1 V, thus defining +2 V at the address of interest. With all the other leads grounded, voltage magnitudes of only +1 V or –1 V are sensed at all the other non-addressed crosspoints. This procedure allows for selective addressing without any 'cross-talk' or 'half-select'. Although eight of the bits failed to work, 56 bits operated, allowing the acronyms DARPA (Figure 10), SRC and CNSI to be written successfully into and read out of the chip in ASCII code. Contrary to standard RAM, where the memory addresses need to be continually rewritten every tens of milliseconds, the metastability of the ON state in these molecular analogues displays half-lives of 15 – 60 minutes.

(Insert Figure 10 here)

1.7.4. Miniaturization of the Crossbar

The ultimate and inevitable evolution of molecular electronics finds its expression in a device defined by a single molecule that switches the conduction between two nanowires. Consequently, the cationically charged analogue to pyrene, diazapyrenium (DAP^{2+}) [48], provided rapid access (Figure 11a) to a switchable [2]catenane $\mathbf{28}^{4+}$ that, when spread onto a water surface using $DMPA^-$ as counterions, formed stable Langmuir monolayers. Devices were fabricated [49] on the nanoscale

using a modification of the general method discussed in ***Section 1.7.1.*** for catenanes. In this case, a single semiconducting SWNT, which was generated on top of an insulating silicon oxide substrate, was identified and wired for electrical connectivity. LB Monolayers of **28**$^{4+}$ were transferred, and topped (Figure 11b) with a monolayer of $DMPA^{-}$ counterions for protection from the Ti/Al top electrodes.

(Insert Figure 11 here)

In keeping with the control studies undertaken on the catenane and rotaxane devices discussed in ***Sections 1.7.1.*** and ***1.7.2.***, two additional controls with respect to **28**$^{4+}$ were introduced. One control utilized just the DAP^{2+}-containing cyclophane with no interlocking counterpart. Another control (**29**$^{4+}$) retains the catenane constitution, but utilizes a macrocyclic polyether that does not possess any switchable character. Only the switchable catenane produces a hysteretic remnant molecular signature, which bears the same form as the one recorded for all of the other devices based on switchable catenanes and rotaxanes. A minor shift in the threshold voltages to +/– 2.5 V for writing the device was required (Figure 11c) to guarantee binary switching activity. The same write-read cycles applied to the degenerate catenane **29**$^{4+}$ produced no changes in the current, displaying a flat featureless trace.

In the context of a single-molecule transistor, break junction devices, coupled with a third gate electrode, have been fabricated [50] using [2]rotaxanes and their dumbbell components. These devices allow the electrical transport through a single molecule to be recorded [51] between two electrodes as a function of the applied bias and gate voltage. In these types of molecular systems, the molecule behaves as a structurally flexible quantum dot, resulting in a resonant tunneling transistor-type device.

A rotaxane **30**$^{4+}$ (Figure 12) with disulfide tethers for attachment to gold, was prepared for these measurements in order to bridge across the break junction. The differential conductance measurements revealed that the signatures observed are dominated by the interface between the rotaxanes and the gold electrodes. This interpretation follows from the observed symmetry in the differential conductance measurements. For **30**$^{4+}$, a symmetric signature is observed. However, in the comparison compound **31**$^{4+}$, in which two different tethering groups are utilized — the disulfide for chemisorption and the tetraaryl stopper for physisorption — the signature is asymmetric. If, however, the differential conductance was dominated by the asymmetric disposition of the molecular components, TTF and DNP, in terms of their location along the dumbbell and electronic character, then, the signature is expected to be asymmetrically displayed for both **30**$^{4+}$ and **31**$^{4+}$. This result is markedly different from all other electronic devices

based on switchable catenanes and rotaxanes, where the observed conductance measurements directly follow the constitution and mechanical movements within the molecules and not from the nature of the stoppers. The observation of this contrasting behavior emphasizes [50] the importance of selecting the electrode materials based, not only on device fabrication requirements, but also on matching the work functions of the molecules and the electrodes.

(Insert Figure 12 here)

While the blueprint for putting some of the world's tiniest molecular machines to work in electronic devices was formed by the interplay of synthetic chemists with device builders, the same theme holds equally well for any advanced technologies to emerge out of fundamental nanoscience in the future. It was this multidisciplinary interaction that saw the development of mechanically operating molecular switches become the focal point for attention and provide for opportunities to broaden their applicability. Whereas the next steps in molecular electronics are likely to be focused on logic [52], the operation of artificial molecular machines is expected to progress on into the realm of mechanical manipulation.

1.8. Mechanical Devices with Molecular Machines

The switchable catenanes and rotaxanes, incorporated in electronic devices that operate as molecular switches, offer the potential to have the switching harnessed in wholly mechanical devices such as actuators [53] and molecular valves [54]. Taking a lesson from biomolecular motors [55] such as myosin and actin in muscle fiber, the production of mechanical force can be extracted from artificial molecular machines that are self-organized on surfaces in order for their cooperative mechanical movements to be amplified and harnessed in nanoelectromechanical systems (NEMS). The first demonstration relies on verifying that the tetracationic cyclophane moves linearly from one donor unit to the other in *closely-packed* condensed phases of bistable rotaxanes on solid substates.

Langmuir monolayers of bistable rotaxanes at the air-water interface and LB monolayers transferred to Si substrates have been investigated [56]. Langmuir monolayers are formed from amphiphilic molecules that are capable of self-organization at the air-water interface [57]. For this purpose, an amphiphilic bistable rotaxane $\mathbf{32}^{4+}$ was prepared (Figure 13a). The long *p*-terphenyl spacer was introduced in order to tune the shuttling barrier and to enhance the rigidity of the rotaxane. This amphiphilic system was found to form Langmuir monolayers readily at the air-water interface [56]. Prior to proceeding with the challenges of switching rotaxanes in compressed monolayers,

the switching properties [27] that are expected to occur in solution were verified [36] by ^{1}H NMR and UV-visible spectroscopies.

(Insert Figure 13 here)

Now that the relative motions of the components in these molecular machines have been demonstrated, the [2]rotaxane molecules were transferred to — and constrained within two dimensions at — the air-water interface. The amphiphilic rotaxane and its dumbbell were studied using Langmuir isotherm techniques in order to establish their ability to form stable monolayers and for their capacity to switch in this type of condensed phase. The simplest approach [45a] relies on the comparison (Figure 13b) of Langmuir layers prepared on neutral and oxidizing subphases. The Langmuir isotherm of the [2]rotaxane **32**$^{4+}$ was recorded with water as the subphase and then again with the standard oxidant, $Fe(ClO_4)_3$ premixed into the subphase. The two isotherms are different. In general, the oxidized molecules in the monolayer appear to occupy a larger mean molecular area compared to the unoxidized form, at almost every pressure. Control Langmuir isotherm experiments performed on the dumbbells display a negligible difference upon oxidation, and hence this behavior, which contrasts with that of the rotaxane **32**$^{4+}$, supports the interpretation that the redox-driven mechanical movement of the tetracationic cyclophane causes the change observed in the rotaxane's isotherm.

In order to provide independent spectroscopic verification for the movement of the cyclophane as a consequence of the oxidizing conditions in the subphase, and, consequently, the influence of the cyclophane's movement on the switched isotherm, X-ray photoelectron spectroscopy (XPS) of the LB monolayers was conducted [56]. The intensity of the photoemisson from the 1s orbital on the nitrogen atoms was recorded for the unswitched and switched LB monolayers transferred to a Si substrate. It was found (Figure 13c) that the relative intensity of the nitrogen signal, and therefore the cyclophane's signal, increased when the oxidant was added to the subphase. The intensity increase was calculated to be equal to a 44% change in height with respect to the monolayer's thickness. The percentage height change is consistent with the cyclophane moving 3.7 nm upwards from the TTF unit to the DNP ring system. By contrast, the dumbbell **33** displayed no signal and an amphiphilic [2]rotaxane $\mathbf{34}^{4+}$ in which the order of the TTF and DNP units were reversed with respect to the SiO_2 substrate, displayed consistent spectroscopic changes.

The ultimate test of mechanical motion of the tetracationic cyclophane in a closely packed monolayer was performed on LB layers transferred to a SiO_2 substrate. For these purposes, a LB double layer of $\mathbf{34}^{4+}$was prepared in order to display a hydrophilic outer surface to the aqueous solution of the oxidant $Fe(ClO_4)_3$, into which the LB double layer was immersed. The XPS data (Figure 13d) display a signal increase that

is consistent with the cyclophane's movement, following exposure to the oxidizing conditions. This experiment provides spectroscopic evidence that, even when amphiphilic bistable [2]rotaxanes are closely packed in the condensed phase of a monolayer, the cyclophane undergoes mechanical movement following oxidation of the TTF unit.

The verification of the linear mechanical movement of the cyclophane within rotaxanes in a LB monolayer provides strong support for developing NEMS devices that incorporate switchable rotaxanes.

An alternative usage for the mechanical movements of $\mathbf{1}^{4+}$ is in the fabrication [54b] of a molecular valve based on a surface-bound pseudorotaxane. The DNP-based thread **26**, when bound to a silica surface, and complexed with $\mathbf{1}^{4+}$, displays [54a] reversible light-driven dethreading and rethreading. From this initial demonstration, the surface-bound pseudorotaxane $[\mathbf{1}\supset\mathbf{26}]^{4+}$ can be localized around the edges of silica nanopores that serve as reservoirs for an iridium-based luminescent dye. Chemically-driven dethreading of $\mathbf{1}^{4+}$ unblocks the pore's opening, leading to a release of the dye and hence the observation of its luminescent signal from the surrounding solution.

1.9. Conclusions

The π-electron deficient tetracationic cyclophane, cyclobis(paraquat-*p*-phenylene) is undoubtedly the central compound and component responsible for the development of a big and important class of

molecular machines. The extensive host-guest studies of complexes of the cyclophane provided an understanding of the thermodynamic factors that allow us to control the relative locations of molecular components in both catenanes and rotaxanes. In other words, such a high level of positional security, resolved down to the subnanometer scale clears the decks for the construction of the linear and rotary motors with the machines' parts fixed in their starting positions. When a second donor unit is introduced, thermodynamic factors are identified that make it possible for the mechanical motions of molecular components to be controlled with enhanced precision. That is, the physical movements back and forth, or around and around, within different types of motors can be controlled to perform their activities at any instant. Whereas relative movements can be stimulated using chemical, electrochemical or photochemical means, it was voltage-gated movements that were utilized in the fabrication of the 64-bit molecular RAM. And so, the practical utility of this unique class of machinery was vindicated and their position, on the shelves of the modern nanomechanic, secured. Finally, the challenges that lie ahead revolve around their potential to be deployed in mechanical devices where their machinations may be liberated from the academic straitjacket of experimental science for the purposes of doing real hard work. Such labor, will not only be operable from the machines' origins at the nanoscale, but also with options to move other objects around across

the scales that reach up to, and possibly into, the world of their macroscopic counterparts — thus bringing their realization back to one of the original sources of inspiration leading to their creation.

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Captions to Schemes

Scheme 1. Synthesis of the tetracationic cyclophane **1**•4PF_6 and the formation of the complex [**1**⊃**4**]•4PF_6.

Scheme 2. Template-directed synthesis of the tetracationic cyclophane **1**•4PF_6.

Scheme 3. The template-directed synthesis of the [2]catenane **8**•4PF_6.

Scheme 4. Dynamic circumrotational processes associated with the [2]catenane **8**$^{4+}$ in solution.

Scheme 5. Self-assembly of the [3]catenane **13**•4PF_6 incorporating an enlarged tetracationic cyclophane.

Scheme 6. The self-assembly of [n]catenanes starting from the [3]catenane **13**•4PF_6.

Scheme 7. Two strategies, a) clipping and b) threading, for making a [2]rotaxane incorporating the tetracationic cyclophane.

Scheme 8. The template-directed synthesis of the molecular shuttle **19**•4PF_6.

Scheme 9. The shuttling process and energy barrier for the movement of the tetracationic cyclophane between the two degenerate recognition sites, A and B, in the [2]rotaxane **19**$^{4+}$.

Scheme 10. The chemically and electrochemically controllable switching of the [2]rotaxane 2**1**$^{4+}$.

Scheme 11. The synthesis of the slow-shuttling [2]rotaxane **22**•4PF_6.

Scheme 12. A [2]catenane **24**$^{4+}$ that can be switched by both chemical and electrochemical means.

Scheme 13. Switching of the [2]rotaxane **25**$^{4+}$.

Scheme 14. The photochemically controllable dethreading/rethreading processes of the pseudorotaxane [**1**⊃**26**]$^{4+}$. Process 1 indicates the photoexcitation of the

photosensitizer **P** and Process 2 indicates the subsequent electron transfer from **P*** to one of the bipyridium units in the cyclophane.

Captions to Figures

Figure 1. Structural formula of the tetracationic cyclophane $\mathbf{1}^{4+}$ and its graphical representation.

Figure 2. Graphical representations of the three primary design motifs of molecular machines.

Figure 3. a) Structure of $\mathbf{1}^{4+}$ in the crystal. b) Space-filling representation of the structure of $\mathbf{1}^{4+}$ in the solid state.

Figure 4. The X-ray crystal structure of the 1:1 complex $[\mathbf{1}\supset\mathbf{4}]^{4+}$.

Figure 5. a) The crystal structure of the [2]catenane $\mathbf{8}^{4+}$ and b) the π-donor/π-acceptor/π-donor/π-acceptor stack formed in the solid state.

Figure 6. The space-filling representation of the X-ray crystal structure of a) Olympiadane $\mathbf{15}^{12+}$ and b) a [7]catenane $\mathbf{18}^{20+}$.

Figure 7. a) An electronic device based on the bistable [2]catenane $\mathbf{24}^{4+}$, b) remnant molecular signature, c) binary switching behavior of device and d) the proposed nanoelectromechanical switching mechanism.

Figure 8. Structural formula and graphical representation of the amphiphilic bistable rotaxane $\mathbf{27}^{4+}$ used in electronic devices.

Figure 9. Graphical representation of the proposed nanoelectromechanical switching mechanism of the amphiphilic bistable rotaxane $\mathbf{27}^{4+}$ in devices.

Figure 10. Demonstration of DARPA written in ASCII code into an 8 x 8 64-bit molecular RAM chip.

Figure 11. a) Structural formula and graphical representation of the bistable [2]catenane **28**$^{4+}$ and b) the device constructed on a carbon nanotube. c) Binary switching behavior in the switchable and degenerate [2]catenanes, **28**$^{4+}$ and **29**$^{4+}$, respectively.

Figure 12. Structural formulas of the "symmetrical" rotaxane **30**$^{4+}$ and the "unsymmetrical" rotaxane **31**$^{4+}$ used in single-molecule transistors.

Figure 13. a) Structural formulas and graphical representations of the amphiphilic rotaxanes **32**$^{4+}$and **34**$^{4+}$, and a dumbbell **33**$^{4+}$. b) In situ Langmuir switching of the monolayers display changes in the c) XPS spectra that correlate with the movement of the tetracationic cyclophane. d) Mechanical movement of the cyclophane in a LB monolayer was correlated with changes in the XPS spectra.